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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,988	08/06/2001	John Dudley Williams	1954-353	6893

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EXAMINER

GAKH, YELENA G

ART UNIT	PAPER NUMBER
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1743

DATE MAILED: 05/29/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/921,988

Applicant(s)

WILLIAMS ET AL.

Examiner

Yelena G. Gakh, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 10 and 11 is/are rejected.
- 7) ☒ Claim(s) 7-9 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claim 1** is rejected under 35 U.S.C. 102(b) as being anticipated by Berkel et al. (Anal. Chem.).

Berkel teaches improvement of analysis of the compounds with electrospray ionization mass spectrometry (ES-MS) by derivatizing analytes, e.g. stigmaterol and pinacol, with ferrocenyl boronate esters (Abstract, page 1546, 1547). He emphasizes: “the nature of the analyte derivative best suited for electrochemical ionization in the ES [electrospray] capillary is one that is easy to oxidize (or reduce) by one-electron transfer to form a predictable, solution-stable ionic species that can survive the transfer from solution to the gas phase during the ES process” (page 1545, left column). Berkel further demonstrates, that ferroceneboronate derivatives of stigmaterol and pinacol, taken as examples of steroids and diols, “will be much easier to oxidize than most organic species found in a typical ES system. Moreover, once oxidized in the ES capillary, the derivative radical cations should be sufficiently stable to survive in solution until sprayed” (page 1547, left column in Results and Discussion”).

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 2-3** are rejected under 35 U.S.C. 103(a) as being unpatentable over Berkel in view of Yang et al. (Chem. Res. Chin., Carbohydrate Chem.) and Desaire et al. (Anal. Chem.).

Berkel does not disclose using ferroceneboronate derivatives specifically for carbohydrates, although he demonstrates the usefulness of using such derivatives for diols, e.g. pinacol.

Yang demonstrates the advantages of using boronic derivatives, including areneboronates, of various mono- and disaccharides for their stereospecific determination by fast atom bombardment mass spectrometry (FAB MS), because boron compounds react stereoselectively with two hydroxyl groups of the saccharides.

It would have been obvious for anyone of ordinary skills in the art to apply Berkel's method to saccharides, because Yang demonstrates efficiency of using areneboronic derivatives of saccharides for FAB mass spectrometric analysis, and ES-MS is more advanced and modern technique of mass spectrometry, for which advantages of using specific boronic compounds, namely ferroceneboronates, are demonstrated by Berkel. As emphasized by Berkel, ferrocene derivatives are easily oxidized in ES capillary (which is not required in an older FAB mass

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spectrometric technique used by Yang), while boron compounds stereospecifically react with saccharides, as indicated by Yang, which makes ferroceneboronates the most obvious derivatives for ES-MS analysis of saccharides.

Berkel in view of Yang do not specifically teach their method for N-acetylated hexose carbohydrates, particularly those recited in claim 3.

Desaire demonstrates the importance of stereospecific detection of various N-acetylated hexose carbohydrates, including those recited in claim 3 (Table 2), by tandem mass spectrometric method, which he applies to complexes of Co or Zn compounds of the carbohydrates.

It would have been obvious for anyone of ordinary skills in the art to apply Berkel-Yang's method to N-acetylated hexose carbohydrates, because N-acetylated hexose carbohydrates are specific group of saccharides possessing OH-groups which can stereospecifically react with boron compounds, with ferroceneboronates being the best derivatives for ES-MS analysis, as taught by Berkel in view of Yang, and because they are important compounds for stereospecific MS analysis, as indicated by Desaire.

7. **Claims 4-6 and 10-11** are rejected under 35 U.S.C. 103(a) as being unpatentable over Berkel in view of Yang.

Berkel does not teach using ferroceneboronate derivatives of specifically saccharides listed in claims 4-6 and 10-11, for ES-MS analysis, although he demonstrates the usefulness of such derivatives for diols.

Yang discloses negative ion FAB mass spectrometry of saccharides, including those recited in claims 4-6 and 10 (glucose, mannose, galactose, fucose, rhamnose, see Table 3, and maltose, cellobiose and lactose, see table 4), using areneboronic acid which stereospecifically reacts with mono- and disaccharides, thus allowing differentiation between various sugars in FAB MS.

It would have been obvious for anyone of ordinary skills in the art to apply Berkel's method to saccharides of claims 4-6 and 10, because Yang demonstrates efficiency of using their areneboronic derivatives for FAB mass spectrometric analysis, and ES-MS is much more advanced and modern technique of mass spectrometry, for which advantages of using specific boronic compounds, namely ferroceneboronates, are demonstrated by Berkel. As emphasized by

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Berkel, ferrocene derivatives are easily oxidized in ES capillary, while boron compounds stereospecifically react with saccharides, as indicated by Yang, which makes ferroceneboronates the most obvious derivatives for ES-MS analysis of saccharides. It would have been obvious to apply this method to O-methyl glycosides, since these are MeO-derivatives of saccharides with unaffected OH-groups of the rings participating in reactions with ferroceneboronates.

### ***Allowable Subject Matter***

8. **Claims 7-9** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: the prior art of Berkel, Yang and Desaire, as well as Gamon et al. (Anal. Sci.),<sup>IDS</sup> disclosing mass spectrometric studies of ferroceneboronate derivatives of various diols, including cholesterol derivatives, and Castro-Perez (ics.pubs.), describing high-sensitive LC-ES-MS-MS analysis of estrogens, including 2- and 4-hydroxyderivatives, does not teach or suggest, alone or in combination, derivatization of catecho estrogens, 2- and 4-hydroxy-estradiols in particular, with ferrocenyl boronate in order to improve their ES-MS detection. These estrogen molecules have two OH-groups in aromatic rings, which makes them different from OH-groups in saccharides, disclosed by e.g. Yang.

### ***Conclusion***

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Brooks et al. (Heterocycles)* discloses GC-MS analysis of ferroceneboronates of various diols and triols, including those of estratriene and androstene; *Takano et al. (Biomed. Env. Mass Spectr.)* disclose "a selected ion monitoring method for quantifying simvastatin and its acid form in human plasma, using the ferroceneboronate derivative"; *Vaisir et al. (Rap. Comm. Mass. Spectr.)* teach derivatization of ecdysteroids to give cyclic phenylboronates for FAB MS analysis.

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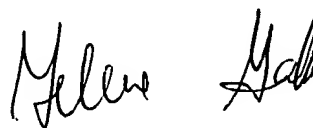
10. The art, which is pertinent to the subject matter of the disclosure but is not the prior art: *Young et al. (Rapid Comm. Mass Spectr.)* discloses "analysis of N-acetylated hexosamine monosaccharides by ferrocenyl boronation and tandem electrospray ionization mass spectrometry"; *Gentili et al. (Chromatographia)* teach "analysis of free estrogens and their conjugates in sewage and river waters by solid-phase extraction then liquid chromatography electrospray-tandem mass spectrometry"; *Xu et al. (J. Chromatog. B)* disclose "stable isotope dilution high-performance liquid chromatography-electrospray ionization mass spectrometry method for endogenous 2- and 4-hydroxyestrogens in human urine".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 10:00am-6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Yelena G. Gakh  
May 23, 2003

Handwritten signature of Yelena G. Gakh in black ink.